Amendments to the Drawings

The attached sheet of drawings includes changes to Figures 4 and 6. These sheets, which include Figures 4 and 6, replace the original sheets, including Figures 4 and 6. In the replacement Figures, SEQ ID NOs representing the sequences as described in the specification, have been included in the figure.

Attachments: 1) Replacement Sheets

2) Annotated Sheets Showing Changes

REMARKS

Amendments to the Specification

Applicants have amended pages 32, 39, 41 and 43 of the specification, in accordance with the Examiner's suggestions, as outlined below.

Page 32 of the specification has been amended to improve its form and delete references to embedded hyperlinks. This amendment brings the specification in compliance with MPEP §608.01.

Table 1 on page 39, Table 2 on page 41 and Table 3 on page 43 of the specification have all been amended to insert a column of sequence identifiers (SEQ ID NOs) to correspond to each sequence identified in the tables. Table 3 additionally comprises a column identifying the SEQ ID NOs that correspond to the reverse complement of each sequence in that table.

None of these amendments adds new matter. All of the sequence identifiers (i.e., SEQ ID NOs) were present in the specification as filed. Entry of these amendments is requested.

The Claim Amendments

Applicants have amended claims 1, 3, 4, 6, 7, 8, 12, 37 and 39, to improve their form and to remove the non-elected subject matter, as described further below. Applicants have cancelled claims 2, 9-11, 14-36 and 38, without prejudice. Applicants make these amendments expressly without waiver of their right to file for and to obtain claims directed to the cancelled or amended subject matter in this application or in divisional or continuing applications claiming priority and benefit herefrom.

None of the claim amendments adds new matter. Their entry is requested. Upon entry of these amendments, claims 1, 3-8, 12, 13, 37, 39 and 40 will be pending in this application.

Drawing Amendments

Applicants have amended Figures 4 and 6 to add the previously omitted sequence identifiers (i.e. SEQ ID NOs), for all of the nucleotide sequences, as requested by the Examiner. All of the added SEQ ID NOs had previously been presented in the sequence listing, thus no new matter has been added and no new sequence listing is required.

All of the amendments to the application drawing are in compliance with 37 C.F.R. §1.84, as detailed above, and have been submitted on replacement sheets of drawings, each titled "Replacement Sheet", as an attachment to the amendment documents. 37 C.F.R. §1.121(d). Marked up copies of the amended figures, including annotations indicating the changes, have been submitted on marked up sheets, each titled "Annotated Sheet Showing Changes", as an attachment to the amendment document. 37 C.F.R. §1.121(d).

None of these amendments adds new matter. They resolve all of the Examiner's objections to the drawings filed on April 8, 2002 as stated in the July 15, 2005 Office Action. Their entry is requested.

The Office Action

Information Disclosure Statement

Applicants acknowledge the Examiner's consideration of the documents submitted in the March 8, 2002 Information Disclosure Statement (IDS). The Examiner notes that the listing of references in the specification is not a proper IDS. Accordingly, applicants will provide a Supplementary Information Disclosure Statement for the Examiner's consideration, which includes all relevant references in the specification, in due course.

Drawings

The Examiner has objected to the Figure 5(b) under 37 C.F.R. §1.83(a) because , in the Examiner's view, it "fails to show which lines represent the wild-type and/or C1229G as described in the specification." Applicants traverse.

The specification describes on page 37 in Example 4 as well as on page 33 in the description of the drawings (see Figure 5 caption), the outcome of the experiment as illustrated in Figure 5(b). As described on page 37 and clearly shown in Figure 5b, a wild-type sample of 404 bp is completely digested by AlwnI so as to result in a 316 bp and a 88 bp fragment (i.e., lane 3), while a heterozygous wild-type/C1229G mutant sample of 404 bp is only partially digested by AlwnI so as to result in a 404 bp fragment (the mutant allele which does not contain the AlwnI restriction site, thus, is not digested in the presence of the AlwnI enzyme), a 316 bp and an 88 bp fragment (the wild-type allele which does contain the AlwnI restriction site and is digested in the presence of the enzyme) (i.e., lane 4). Lanes 1 and 2 represent control conditions for the two samples (wild-type/wild-type and wild-type/mutant) showing that no sample is digested in the

absence of the AlwnI enzyme. These results are clearly understood by viewing the four lanes of the Alwn1 restriction digest showing the wild-type/wild-type and wild-type/C1229G mutant without (lanes 1 and 2) and with addition of the enzyme AlwnI, as indicated by "-Alwn1" and "+Alwn1" in the figure, respectively. Applicants respectfully request that the Examiner reconsider and withdraw the objection.

Specification

The Examiner objects to pages 39 (Table 1), 41 (Table 2), 43 (Table 3), 44-45 (Table 4), Figures 4 and 6 under 37 C.F.R. §§ 1.821-1.825 for improper disclosure of nucleotide sequences without a respective sequence identifier, i.e., SEQ ID NOs. The Examiner also objects to page 32, 3rd paragraph, for improperly containing an embedded hyperlink and/or other form of browser executable code. MPEP § 608.01

In response, applicants have amended pages 39, 41, 43-45 and Figures 4 and 6 to include sequence identifiers for each sequence listing in the tables and figures. Applicants have also amended page 32 of the specification to delete references to embedded hyperlinks, in accordance with the Examiner's suggestion.

Claim Objections

Claims 1-8, 12-13, 37 and 39-40 stand objected to as reciting non-elected nucleotide sequence identifiers and/or polynucleotides which encode a CYP3A4 or CYP3A7 polypeptide. Claim 37 is further objected to as being dependent from a non-elected invention.

Applicants have obviated the Examiner's rejection by amending claims 1, 3, 7 and 8 to delete all references to a CYP3A7 polypeptide, gene, or protein, and to a polynucleotide which encodes a CYP3A7 polypeptide. Applicant has directed amended claim 1 (and claims 3, 7 and 8 which depend therefrom) to an isolated polynucleotide encoding a variant cytochrome P450 3A4 (CYP3A4) monooxygenase polypeptide or fragment thereof that comprises a specific nucleotide sequence or encodes the corresponding amino acid sequence. Applicants have incorporated the subject matter of claim 2 into claim 1 and have thus cancelled claim 2. Applicants have amended claim 37 to delete the back reference to a non-elected claim and recite a primer or probe consisting of an oligonucleotide of about 15 to 50 nucleotides in length and comprising the nucleotide sequence of SEQ ID NO:90 or a complementary sequence. Applicants have amended claim 39 to delete all back references to non-elected and cancelled claims and to correct improper multiple dependencies.

Claim Rejections

35 U.S.C. §101 – Patentable Subject Matter

Claims 1-2, 6 and 12 stand rejected under 35 U.S.C. § 101 for failing to sufficiently distinguish the claims over naturally-occurring polynucleotides and/or host cells and not pointing out any non-naturally occurring differences between the claimed products and the naturally occurring products. The Examiner suggests amending the claims to recite "isolated" or "purified", to indicate the hand of the inventor.

Applicants have cancelled claim 2 and incorporated the subject matter of the claim into amended claim 1. The rejection as to claim 2, thus, is obviated. Applicants have

amended claims 1, 6 and 12 to recite an isolated polynucleotide, an isolated host cell, and an isolated nucleic acid molecule, respectively. Support for these amendments can be found throughout the specification, e.g., at page 15, 1st paragraph.

35 U.S.C. § 112, Second Paragraph - Indefiniteness

Claims 2-8, 12-13, 37 and 39-40 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to point out and distinctly claim the subject matter of the invention. The Examiner states that the claims are vague and indefinite for reciting the term "CYP3A4" or "CYP3A7" as the sole means of identifying the claimed molecule. The Examiner suggests amending the claims to specifically and uniquely identify CYP3A4 or CYP3A7 by, e.g., reciting SEQ ID NOs and function of the claimed molecule.

Applicants have obviated the Examiner's rejection in part by deleting all references to a CYP3A7 polypeptide, gene, or protein, and to a polynucleotide which encodes a CYP3A7 polypeptide. Applicants also have cancelled the claim to a polynucleotide with any nucleotide deletion, addition and/or substitution thereof, wherein said polynucleotide encodes a genus of variant polypeptides and/or fragments thereof referred to as CYP3A4 or CYP3A7.

The subject matter of the remaining claims is based on applicants' discovery of phenotypic change associated with an amino acid substitution that results from a specific nucleotide change in a variant of the cytochrome P450 3A4 (CYP3A4) monooxygenase gene. Applicants have amended claim 1 (from which the remaining claims all depend) to characterize CYP3A4 as the "cytochrome P450 3A4 monooxygenase". Support for this amendment is

provided, e.g., on page 2, 3rd paragraphs of the specification, which describes the CYP3A4 monooxygenase as being the predominant cytochrome P450 in human liver and small bowel.

The specification also refers to the sequence of CYP3A4 by GenBank accession number AF280107. This accession number provides public access to the gene sequence of CYP3A4 and describes the gene as "Homo sapiens cytochrome P450 polypeptide 4 (CYP3A4)". The claims are based on applicants discovery that a variant CYP3A4 containing a change from threonine (T) to methionine (M) at residue 363 resulting from a polymorphism at nucleotide position 21867 of the CYP3A4 gene (GenBank Accession No.: AF280107, wherein the nucleotide A of the first ATG encoding the CYP3A4 protein has been numbered +1) (*See, e.g.*, page 43, Table 3; and page 6, 1st paragraph of the specification) results in impaired expression and enzymatic activity compared to the wild type CYP3A4 protein. A portion of the CYP3A4 nucleotide sequence containing this polymorphism is provided in SEQ ID NO:90.

A skilled worker would thus readily understand what is meant by CYP3A4 in the pending claims as amended. Applicants therefore request that the Examiner reconsider and withdraw this objection.

35 U.S.C. § 112, First Paragraph – Written Description

Claims 2-8, 12-13 and 39-40 stand rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking written description. Specifically, the Examiner states that the claims include a genus of polynucleotides having the nucleic acid sequence of SEQ ID NO:90 and/or any nucleotide deletion, addition and/or substitution thereof, wherein said polynucleotide encodes a genus of variant polypeptides and/or fragments thereof referred to as CYP3A4 or

CYP3A7. The Examiner contends that the specification does not provide a representative number of variant CYP3A4 or CYP3A7 proteins and/or fragments that encompass the genus of polypeptides or the representative number of nucleotides that encompass the genus of polynucleotides having a nucleotide sequence of SEQ ID NO:90 which encode a variant. Applicants traverse, in view of the claim amendments and below remarks.

Applicants' incorporation of claim 2 into amended claim 1 obviates the Examiner's rejection as to claim 2. Claims 3-8, 12-13, 27 and 39-40, as amended, are directed to an isolated polynucleotide encoding a variant CYP3A4 polypeptide or fragment thereof. Every member of the genus of claimed polynucleotides encodes a variant CYP3A4 polypeptide or a fragment of said polypeptide, and shares a common structural feature -- the nucleotide sequence of SEQ ID NO:90, which includes the above-described nucleotide polymorphism. But applicants provide even more than this – they also demonstrate the function corresponding to this structural feature shared by all members of the claimed genus, i.e., the impaired expression resulting from the T to M change encoded by the nucleotide sequence in SEQ ID NO:90.

More particularly, the instant application discloses, on pages 38-39, Example 6, the functional consequences of specific protein variants of CYP3A4. The application teaches that the variant CYP3A4 holoenzyme containing the T to M change at residue 363 ("T363M") has a diminished expression, at levels less than 10% of the wild-type CYP3A4, as assessed by measuring reduced CO difference spectra. *See*, the M5 variant on page 38, Example 6. The M5 variant corresponds an CYP3A4 variant having the nucleic acid sequence of SEQ ID NO:90. *See, e.g.,* page 44, Table 4, the first variant in exon 11, wherein the mutated sequence is SEQ ID NO:90. The expression of that M5 variant also exhibited a reduced expression as assessed by

Western Blotting using an anti CYP3A12 polyclonal antibody known to cross-react with CYP3A4. *See*, Figure 7, showing an immunoblot of wild-type CYP3A4 and the M5 variant, where the variant has a faint 54 kDA band compared to the wild-type.

The catalytic activity of the M5 variant was also strongly impaired by measurement with testosterone, progesterone and 7-benzyloxy-4-(trifluoromethyl)coumarin (7-BFC). In the presence of each of these substrates, the M5 variant displayed an activity that was approximately half that of the wild-type protein. See, e.g., page 39, lines 3-4 and Tables 5-7 showing testosterone hydroxylase activity, progesterone hydroxylase activity and 7-BFC debenzylase activity of wild-type and mutant CYP3A4 mutants (including M5), respectively.

The instant application teaches a structure/function relationship for the shared structural feature of the claimed polynucleotides. The written description requirement, thus, has been met. Applicants therefore request that the Examiner reconsider and withdraw this rejection.

35 U.S.C. § 112, First Paragraph – Enablement

Claims 6-8 and 39-40 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Specifically, the Examiner contends that the composition and method claims read on a cell within a transgenic animal given that the term "isolated" is not denoted in describing the transgenic cell. The Examiner states that applicants can obviate the rejection by amending the claims to recite the term "isolated" before the recitation of "host cell". As noted *supra*, claim 6 and the claims that depend directly or

indirectly from it now refer to an "isolated" host cell. Accordingly, applicants request that the Examiner withdraw this rejection.

35 U.S.C. §102(e) - Anticipation

Claims 1, 4-6, 8, 12-13, 37, and 39-40 stand rejected under 35 U.S.C. §102(e) as being anticipated by Larossa et al., U.S. Patent 6,025,131 ("Larossa"). According to the Examiner, the patent teaches a polynucleotide having the nucleotide sequence of SEQ ID NO:90, as well as a vector comprising the polynucleotide, host cells with a vector, a nucleic acid molecule complementary to the polynucleotide, a diagnostic composition comprising the polynucleotide, and a method for producing cells comprising the polynucleotide. Applicants traverse, in view of the claim amendments and the below remarks.

Amended claim 1 recites an isolated polynucleotide encoding a variant CYP3A4 polypeptide or fragment thereof. The sequence* referred to by the Examiner in Larossa is not a polynucleotide encoding a variant CYP3A4 polypeptide or fragment thereof. Instead, the Larossa sequence is derived from a genomic segment isolated from *E. coli* and said to be a 205 base pair sequence that borders a sulfometuron methyl (SM) responsive regulatory region in an unknown protein. *See*, e.g., column 4, lines 30-38. Thus the Larossa sequence cannot anticipate the subject matter of the amended claims. Applicants therefore request that the Examiner reconsider and withdraw this rejection.

* The Examiner refers to an attached sequence comparison for the sequence alignment of SEQ ID NO:90 with sequence identifier 12 of Larossa. Applicants note that they did not receive any attachment with a sequence comparison accompanying the Office Action.

Conclusion

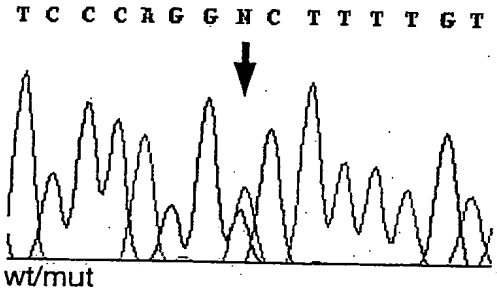
Applicants request favorable consideration and early allowance of the elected claims.

Respectfully submitted,

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CYP3A4 polymorphisms

Exon 3 (G6004A; Gly56Asp)

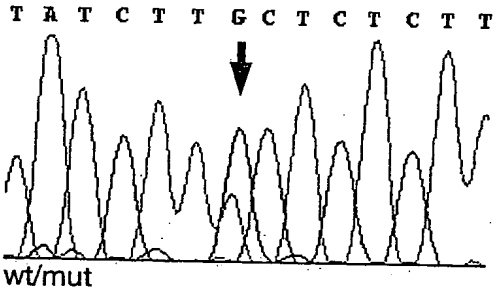


wt/mut

Oligonucleotide 3A450F (forwards)

SEQ ID : 52 (*rev. 53)

Intron 7 (T→G)

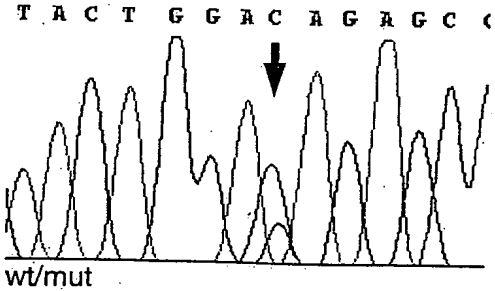


wt/mut

Oligonucleotide 3A433F (forwards)

SEQ: ID 58 (rev. 59)

A CYP3A7 exon 11 polymorphism (C1229G; Thr409Arg)



wt/mut

Oligonucleotide 3A742F (forwards)

SEQ ID : 124

*rev: reverse complement

Fig. 4

CYP3A4

Exon 3 (g.6004G>A, G56D) SEQ ID: 128

CCTCTAACTGCCAGCAAGTCTGATTTCATTGGCTTCGACTGTTTTCAT→CCCCAATTAGAGGCAG
GGTTAAGTACATTAAAAATAATAATCAAATATTATTTTGTTTCTCCTCCCAGGG→ACTTTTGTATGT
TTGACATGGAATGTCATAAAAAGTATGGAAAAGTGTGGGGGTGAGTATTCTGGAAACTTCCATT
GGATAGACTTGTTTCTATGATGAGTTTACCCCACTGCACAGAGGACAGTCTCAGCCC

Exon 4 (Primer 3A4-52F and 3A4-37R) SEQ ID: 130

AGTCTGGCTTCCTGGGTTGGGCTCCAGCTGTAGAATAAGGCTGTTGATGTTTAA
TCAACTCTGTTTTTTTCACACAGCTTTTATGATGGTCAACAGCCTGTGCTGGCTA
TCACAGATCCTGACATGATCAAAACAGTGCTAGTGAAAGAATGTTATTCTGTCT
TCACAAACCGGAGGGTAAGCATTCATGTGTTGAAATTAAAATACTGATTGATTAA
ATTTATATTTTGAAATTCTTATATATTCATAGACAGTTGCCTAAAAAATGTCCAGG
AAGGTTCCACGTCCACTTC

Exon 5 SEQ ID: 132

CTACAACCATGGAGACCTCCACAACTGATGTAGGACAAAATGTTTCTGCTTTGAA
CTCTAGCCTTTTGGTCCAGTGGGATTTATGAAAAGTGCCATCTCTATAGCTGAG
GATGAAGAATGGAAGAGATTACGATCATTGCTGTCTCCAACCTTCACCAGTGG
AAAACTCAAGGAGGTATGAAAATAACATGAGTTTTAATAAGAAACTTAAAGAATG
AATCTGGTGGGGACAGGTA

Exon 7 (g.15753T>G) SEQ ID: 134

GTCTGTCTTGACTGGACATGTGGCTTTCCTGATGCACGCATAGAGGAAGGATGG
TAAAAAGGTGCTGATTTTAATTTTCCACATCTTTCTCCACTCAGCGTCTTTGGGG
CCTACAGCATGGATGTGATCACTAGCACATCATTTGGAGTGAACATCGACTCT
CTCAACAATCCACAAGACCCCTTTGTGGAAAACACCAAGAAGCTTTTAAGATT
TGATTTTTTGGATCCATTCTTTCTCTCAATAAGTATGTGGACTACTATTTCCTTTT
ATTTATCTTT→GCTCTCTTAAAAATAACTGCTTTATTGAGATATAAATCACCATGT
AATTCATCCACTTAAAATATACAGTTCAGTGATTTGTAGTACATTTGAAGATATGT
GTGACCATCATC

Exon 9 SEQ ID: 136

GGAGATCAAGGACCACGCTTGTGATTTACTTCTGACTTCAGGAGCCACTTTCTG
TCAGTGAAATTTCTCTTTTTGCTTCTAGCACCGAGTGGATTTCCTTCAGCTGATG
ATTGACTCTCAGAATTCAAAAGAAACTGAGTCCCACAAAGGTAACCAGAGTGT
TTCTGAGGGCTACTTGTGGGGCACTCAGAGGGAAGGCCTTGTTCTGAAAATGTG
CAGGAAGTATTCCAGGATGATGAG

CYP3A7

Exon 11 (C1229G Thr409Arg polymorphism) SEQ ID: 138

CCAGTATGAGTTGTTCTCTGGAACTTCTAACAGTTCAACAGTACTACATGGACTG
AGTTAAAAGTTAATTCAAAAATCTCAATTTATCCAAATCTGTTTCTTTCTTTTCAGG
CACCACCCACCTATGATACTGTGCTACAGTTGGAGTATCTTGACATGGTGGTG
AATGAAACACTCAGATTATTCCCAGTTGCTATGAGACTTGAGAGGGTCTGCAA
AAAAGATGTTGAAATCAATGGGATGTTTATTCCCAAAGGGGTGGTGGTGATGA
TTCCAAGCTATGTTCTTCATCATGACCCAAAGTACTGGAC→GAGAGCCTGAGA
AGTTCCTCCCTGAAAGGTAGGAGGCCCCTGGGAAGGGAGCCCTCCCTGAACC
AGCCTGGTTCAAGCATATTCTGCCT

Fig. 6

CYP3A4 SEQ ID : 143

Exon 4 (Primers 3A4-52F and 3A4-100R)

AGTCTGGCTTCCTGGGTTGGGCTCCAGCTGTAGAATAAGGCTGTTGATGTTTAA
TCAACTCTGTTTTTTTCACACAGCTTTTATGATGGTCAACAGCCTGTGCTGGCTA
TCACAGATCCTGACATGATCAAAACAGTGCTAGTGAAAGAATGTTATTCTGTCT
TCACAAACCGGAGGGTAAGCATTCATGTGTTGAAATTAAAATACTGATTGATTAA
ATTTATATTTTGAAATTCTTATATATTCATAGACAGTTGCCTAAAAAATGTCCAGG
AAGGTTCCACGTCCACTTCATCCTGTCCCC

Exon 5 (g.13908G>A, R130Q) SEQ ID : 144

CTACAACCATGGAGACCTCCACAACTGATGTAGGACAAAATGTTTCTGCTTTGAA
CTCTAGCCTTTTGGTCCAGTGGGATTTATGAAAAGTGCCATCTCTATAGCTGAG
GATGAAGAATGGAAGAGATTACG→AATCATTGCTGTCTCCAACCTTCACCAGT
GGAAAACTCAAGGAGGTATGAAAATAACATGAGTTTTAATAAGAAACTTAAAGA
ATGAATCTGGTGGGGACAGGTA

SEQ ID: 146

Exon 6 (g.14292G>A, V170I; g.14304G>C, D174H; g.14323C>T; g.14329G>T; g.14357T>G)

CCCTTTCCAAGGGGTAGTCCACTGAATTTGAGCTGCCTAAAAATGGTCTTTTATC
TTTATGTACAGAAAACACATCACAAAATTCATTATAAAATGTCACTTACTGCTCCA
TGCTGGGGAAAGCCATGTCCTTCTGGGACTAGAGTCTGCACATTTAACTATGGG
TGGTGTTGTGTTTTGTGCTTAG**ATGGTCCCTATCATTGCCCAGTATGGAGATGT**
GTTGGTGAGAAATCTGAGGCGGGAAGCAGAGACAGGCAAGCCTG→A**TCACC**
TTGAAAG→C**AGT**AAGTAGAAGCGCAGCC→TATGGGG→TTTCTGAGCTGTCAT
GAACCCCTCCAGCT→GGCCTGCCATGGAGCTGATATTCCTGCTGTTGGGTTAT
TCCAGTGACCAGAC

Exon10 (g.20230G>A) SEQ ID: 148

CCCAGTGTACCTCTGAATTGCTTTTCTATTCTTTTCCCTTAGGGATTTGAGGGCT
TCACTTAGATTTCTCTTCATCTAAACTGTGATGCCCTACATTGATCTGATTTACCT
AAAATGTCTTTCCTCTCCTTTCAG**CTCTGTCCGATCTGGAGCTCGTGGCCCAAT**
CAATTATCTTTATTTTTGCTGGCTATGAAACCACGAGCAGTGTTCTCTCCTTCAT
TATGTATGAACTGGCCACTCACCCTGATGTCCAGCAGAAACTGCAGGAGGAA
ATTGATGCAGTTTTACCCAATAAGGTGAGTGGATGG→ATACATGGAGAAGGAG
GGAGGAGGTGAAACCTTAGCAAAAATGCCTCCTCACCACTTCCCAGGAGAATTT
TTATAAAAAGCATAATCACTGATTCTTTCACTGACTCTATGTAGGAAGGCTCTG

Exon 11 (g.21867C>T, T363M; g.21868G>A; g.21896C>T, L373F; g.22026C>T, P416L; g.22041C>T;) SEQ ID: 154

CAGTATGAGTTAGTCTCTGGAGCTCCTAATACTTCATTAGTACTGCATGGACTGA
GTTAAAAGTTAATTCAAAATCTCAATTTATCCAAATCTGTTTCGTTCTTTCCAG**GC**
ACCACCCACCTATGATACTGTGCTACAGATGGAGTATCTTGACATGGTGGTGA
ATGAAAC→TG→A**CTCAGATTATTCCCAATTGCTATGAGA**C→T**TTGAGAGGGT**
CTGCAAAAAAGATGTTGAGATCAATGGGATGTTCATTCCCAAAGGGGTGGTGG
TGATGATTCCAAGCTATGCTCTTCACCGTGACCCAAAGTACTGGACAGAGCCT
GAGAAGTTCCTCCC→T**TGAAAG**GTACAAGGC→TCCCTGGGAAGGGAGCCCTC

Fig. 6 cont.

CCTGAACCAGCCTGGTTCAAGCATATTCTGCCTCTCTTAATCTACAGGACAGTCA
TGTGGTTGTATAATTATTTGCTTGTATTTTTATATTTAGAGATTTTTTTAATCATCA
AATTGATTATTGTCACACTTTACAAACCATAGACTAGAAAAAAGAAAACTACAGTC
ATCCACAATTCCAACAACTTACGATGAAGGTCATCAGTTATG

Exon 12 (g.23081C>T) SEQ ID: 162

CCTGTGTACTACTAGTTGAGGG GTGGCCCCTAAGTAAGAAACCCTAACATGTAA
CTCTTAGGGGTATTATGTCATTAACTTTTTAAAAATCTACCAAC→TGTGGAACCA
GATTCAGCAAGAAGAACAAGGACAACATAGATCCTTACATATACACACCCTTT
GGAAGTGGACCCAGAAACTGCATTGGCATGAGGTTTGCTCTCATGAACATGAA
ACTTGCTCTAATCAGAGTCCTTCAGAACTTCTCCTTCAAACCTTGTAAAGAAAC
ACAGGTTAGTCAATTTTCTATAAAAATAATGTTGTATTAATAATTCTTTTAACTGA
GTGGTCTGTATTTTTTAAAAAGAATATGCTTGTTTAATCTTTTACTAATTTGTTCTC
TGGGCCAAAGAATCAATTAGGCCCATCTGTG

this oligonucleotide used for genotyping differs from the genomic sequence at the positions shown in italics

Exon 13 (g.25925C>T; g.25958T>G) SEQ ID: 163

GGAGTGTCTCACTCACTTTGATGCTATACTTTCTACTTTTGTTTATTTAATGCTTC
TCAATATGCTTGTTTAACTGTTGCAG**ATCCCCCTGAAATTAAGCTTAGGAGGAC**
TTCTTCAACCAGAAAAACCCGTTGTTCTAAAGGTTGAGTCAAGGGATGGCACC
→T**GTAAGTGGAGCCTGA**ATTTTCCTAAGGACTTCT→GGCTTTGCTCTTCAAGAA
ATGAAGATGGGCTTCATCCA

Fig. 6 cont.